

# A Cohort Study of Thyroid Cancer and Other Thyroid Diseases after the Chernobyl Accident: Objectives, Design and Methods

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## INTRODUCTION

**Chernobyl Thyroid Diseases Study Group of Belarus, Ukraine, and the USA. A Cohort Study of Thyroid Cancer and Other Thyroid Diseases after the Chernobyl Accident: Objectives, Design and Methods. *Radiat. Res.* 161, 481–492 (2004).**

The thyroid gland in children is one of the organs that is most sensitive to external exposure to X and  $\gamma$  rays. However, data on the risk of thyroid cancer in children after exposure to radioactive iodines are sparse. The Chernobyl accident in Ukraine in 1986 led to the exposure of large populations to radioactive iodines, particularly <sup>131</sup>I. This paper describes an ongoing cohort study being conducted in Belarus and Ukraine that includes 25,161 subjects under the age of 18 years in 1986 who are being screened for thyroid diseases every 2 years. Individual thyroid doses are being estimated for all study subjects based on measurement of the radioactivity of the thyroid gland made in 1986 together with a radioecological model and interview data. Approximately 100 histologically confirmed thyroid cancers were detected as a consequence of the first round of screening. The data will enable fitting appropriate dose–response models, which are important in both radiation epidemiology and public health for prediction of risks from exposure to radioactive iodines from medical sources and any future nuclear accidents. Plans are to continue to follow-up the cohort for at least three screening cycles, which will lead to more precise estimates of risk. © 2004 by Radiation Research Society

A number of epidemiological studies have shown that exposure to external X and  $\gamma$  radiation is associated with an increased incidence of thyroid cancer. The radiation-associated risk increases approximately linearly with dose, and the magnitude of increase is modified by age at exposure, being higher for children than for adults (1). A combined analysis of seven studies by Ron *et al.* (2) showed that for subjects irradiated under the age of 15 years, the excess absolute risk (EAR) was 4.4 cancers/10,000 person-years (PY) Gy and the excess relative risk (ERR) was 7.7/Gy. External irradiation has also been reported to be associated with autoimmune thyroiditis, hypothyroidism and hyperparathyroidism (3, 4).

Because of its ability to concentrate iodine and incorporate it into thyroglobulin, the thyroid gland is particularly at potential risk from internal irradiation with radioactive isotopes of iodine. There has been considerable interest in nodule and cancer risk after exposure to <sup>131</sup>I, particularly among children, potentially the most sensitive group. Data

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have been reported from long-term follow-up studies of patients receiving this radionuclide for diagnostic or therapeutic purposes. In general, the diagnostic studies have included too few children to provide reliable estimates of risk in children (5, 6). In two large studies of hyperthyroid patients treated with therapeutic doses of  $^{131}\text{I}$ , there was no significantly increased risk of thyroid cancer (7, 8). However, the subjects were mostly adults, and it is uncertain to what extent the results were influenced by pre-existing thyroid disease. Furthermore, the aim of those treatments was to destroy the thyroid, and thus few living cells remained. The most recent studies of hyperthyroid patients from the UK, however, showed a significantly increased risk of thyroid cancer after treatment with  $^{131}\text{I}$  (9, 10).

The risk of thyroid disease resulting from exposure to atmospheric radioactive fallout is more complicated, primarily because of the difficulties encountered in reconstructing radiation doses. The EAR of thyroid cancer among Marshall Islanders exposed to the Bikini nuclear weapons tests was 1.1 and 1.3 cases/10,000 PY Gy for children under 18 years of age and for adults, respectively (11). The Marshall Islanders were exposed to  $^{131}\text{I}$  and short-lived radioactive iodines, but their thyroid doses also had substantial contributions from external  $\gamma$  radiation. Studies from the Nevada Test Site have shown a significant increase in thyroid neoplasms (benign and malignant combined) in those irradiated as children, though the increase is not statistically significant for thyroid carcinomas (12–15).

Thus epidemiological evidence relating exposure to radioactive iodines and risk of thyroid cancer in children is very limited compared to the corresponding data for external exposure to X and  $\gamma$  rays. Risks from radioactive iodines are important in public health both because of the medical uses of  $^{131}\text{I}$  and because radioactive iodines are potentially one of the more important releases from nuclear facility accidents.

The exposure of a large population to radioactive fallout from the Chernobyl nuclear power plant accident in Ukraine on April 26, 1986 was a major disaster from the public health, social and economic perspectives. Nevertheless, it has created an opportunity to examine the effects of radioiodines (mainly  $^{131}\text{I}$ ) on the thyroid gland, especially in children. Initial reports showed a large increase in the observed number of thyroid cancers among those exposed as children beginning 4 years after the accident in Belarus, Ukraine and the Russian Federation (16–18), and this increase has continued to be observed. However, the quantitative contribution of radiation to this increase remains to be definitively determined, since other factors such as population screening programs for thyroid cancer may well have also contributed to this increase.

A case-control study of 107 thyroid cancer cases in children has been conducted in Belarus (19). The primary objective was to assess the relationship between dose to the thyroid and incidence of thyroid cancer. Approximate individual doses were estimated based on ground deposition

of  $^{137}\text{Cs}$ , ground deposition of  $^{131}\text{I}$ , a data bank of 1986 thyroid radiation exposure measurements, questionnaires and interviews. Though no formal dose-response analysis was presented, since it was considered that the doses were too imprecise for such analysis, nevertheless, risk increased monotonically with preliminary dose group, with the odds ratio in the highest dose group (1.0+ Gy) compared to the lowest (<0.3 Gy) being generally of the order of fivefold.

A carefully conducted ecological study has been reported relating incidence of thyroid cancer in children in Belarus and Russia to a mean estimated population dose for the geographic area in which they lived in 1986 (20). Specific incidence risk estimates were reported from this study with values of 2.1 cases/10,000 PY Gy for the EAR and 23/Gy for the ERR. The former is about one-half the corresponding value reported by Ron *et al.* (2) for exposure to external X and  $\gamma$  rays. The ERR is much higher than that reported by Ron *et al.* (2), but it is statistically unstable due to uncertainty in the background incidence rate. This study attempted to account for screening using ecological measures of screening practices, but it was subject to the usual limitations of ecological studies in that individual dose estimates and individual screening practices could not be accounted for.

The present cohort study is designed to provide evidence to supplement that contained in these earlier reports. Two arms of the study using very similar designs are being conducted in Belarus and Ukraine with a total cohort size of 25,156 subjects who were under the age of 18 years at the time of the accident. They are being screened at 2-year intervals for thyroid diseases, with one screening cycle taking 2 years to complete for the entire cohort. (In Belarus, as described subsequently, some subjects are screened yearly to comply with Ministry of Health regulations.) Individual radioactivity measurements of the thyroid gland in 1986 are available for all study subjects and will be used in the estimation of individual thyroid doses. An evaluation will be made of the contributions to thyroid dose from  $^{131}\text{I}$ , other short-lived radioiodine isotopes, and protracted external and internal irradiation, principally  $\gamma$  radiation from  $^{134}\text{Cs}$  and  $^{137}\text{Cs}$ . The study is being conducted by Belarussian and Ukrainian scientists in collaboration with each other and with scientists from the United States.

### Research Objectives

The primary objective of this epidemiological study is to examine the relationship between exposure to radioactive fallout from the Chernobyl accident, particularly  $^{131}\text{I}$  and other radioactive isotopes of iodine, and risk of thyroid cancer while taking into account the effect of screening for such cancers. Specifically, the aims are to:

1. Test the hypothesis that such exposure is positively related to increased risk of thyroid cancer incidence.
2. Develop any corresponding quantitative dose-response relationship.

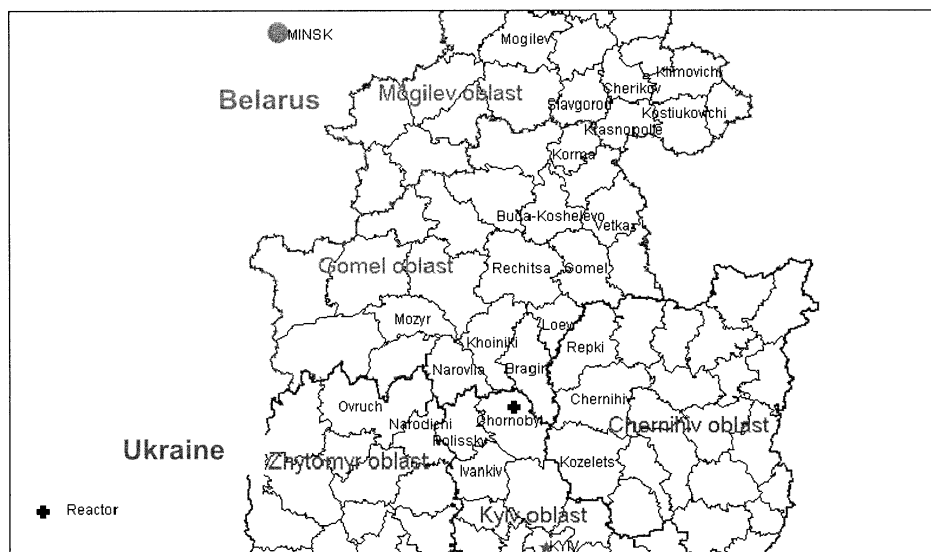


FIG. 1. Areas of Belarus and Ukraine that were contaminated by the Chernobyl accident and are involved in the study.

3. Examine whether any dose-response relationship is modified by host and other factors such as gender, age at exposure, and the ingestion of prophylactic potassium iodide shortly after the accident. It should be noted that such interaction tests would inevitably have less power than tests of main hypotheses.
4. Compare risks per unit dose with the corresponding risks which have been estimated for exposure to external radiation; i.e., estimate the relative biological effectiveness of the two types of radiation in inducing thyroid cancer.<sup>3</sup>
5. The study also has similar objectives with respect to risk of benign thyroid nodules, hyperthyroidism and hypothyroidism.
6. Supplementary objectives include the detection of hyperparathyroidism and autoimmune thyroiditis and the determination of any relationship of these entities to thyroid dose.

## SUBJECTS AND METHODS

### *The Cohort*

The source population for the cohort consisted of 114,537 individuals who were born between April 26, 1968 and April 26, 1986, and who had their thyroid radioactivity measured in 1986 shortly after the accident. These individuals were resident in 1986 in one of a number of highly contaminated areas of Belarus or Ukraine, shown in Fig. 1.

<sup>3</sup> The term relative biological effectiveness (RBE) is used in this paper to indicate the relative efficiency of radioactive iodines compared to external  $\gamma$  and X rays in inducing thyroid cancer. Specifically, it is defined as the ratio of the excess relative risk per gray (or excess risk per 10,000 PY Gy) from radioactive iodines to the corresponding risks from exposure to  $\gamma$  and X rays. Risks for both iodines and  $\gamma$  and X rays depend upon the exact nature of such radiation, e.g., the proportion of short-lived isotopes in the radioactive iodines or the energy of the X or  $\gamma$  rays. Therefore, the RBE would in turn depend upon these factors. Empirically, in the present paper, we define the RBE as the ratio of risks which will be estimated from the present study to the risks reported by Ron *et al.* (2) or any future updating of those risks.

The original file of dose measurements contained information about surname, initials, year of birth (sometimes with month and day of birth), and address in 1986. For some individuals, several dose measurements were made in 1986, and these repeated measurements will be used in the estimation of their individual thyroid doses for the present study.

There were a total of 114,537 records on the dose file for the source population, 39,188 in Belarus and 75,349 in Ukraine. Some effort was made in Belarus to identify multiple records for the same individual on the dose file before tracing started, but no such effort was made in Ukraine. Table 1 shows the distribution of the records for the source population by preliminary thyroid dose category, the preliminary doses being estimated from the activity measurements.

It was decided to study a cohort sampled from the source population more intensively. The primary goals of this more intensive examination were to (1) obtain more detailed and up-to-date information on subjects, particularly that relating to improvement in individual dose estimates, (2) ensure as far as possible that the intensity of thyroid screening within the sample was independent of dose, and (3) conduct active follow-up of study subjects. This examination was limited to this cohort, rather than the whole source population, because of resource and financial limitations. Those individuals who participated in at least the first screening cycle, in total 25,161 individuals (11,918 in Belarus and 13,243 in Ukraine), are designated as the cohort to distinguish them from the source population.

The study was reviewed and approved by the special studies institutional review board (IRB) of the U.S. National Cancer Institute and IRBs for the institutions in Belarus and Ukraine conducting the studies. Any protocol changes must be reviewed and reapproved by all three boards.

### *Tracing Potential Study Subjects*

As discussed subsequently, power calculations indicated that approximately 12,000 subjects in each country would be required for the cohort. To allow for failure to trace potential subjects and for non-participation by traced subjects, it was necessary to attempt to trace all members of the source population in Belarus. In Ukraine, all subjects in the highest dose group were included. In addition, a sample of subjects with preliminary doses below 1 Gy was selected. The numbers in the two lower dose groups were chosen so as to give expected risk estimates with approximately equal degrees of precision in the two groups (see the section on *Power Estimates* for details).

In total, 39,188 records from the dose file were selected for Belarus

**TABLE 1**  
**Distribution of the Source Population, Sample Selected for Tracing and Recruitment, the Examined Cohort, and Unscreened Subjects by Category of Preliminary Thyroid Dose<sup>a</sup>**

	Dose group (Gy)					
	Ukraine				Belarus	
	<0.3	0.3 ≤ D < 1.0	≥1.0	Total	<0.3	0.3 ≤ D < 1.0
Source population (records)	46,533	18,741	10,075	75,349	19,731	11,022
Sample selected for tracing and recruitment (people)	15,391	8,242	8,752	32,385	19,563	10,830
(percentage of source population)	33%	44%	87%	43%	99%	98%
Examined cohort	6,142	3,485	3,616	13,243	4,998	3,380
(percentage of sample selected for tracing and recruitment)	40%	42%	41%	41%	26%	31%

<sup>a</sup> See section on *Dosimetry* for details of preliminary dose estimation.

and 34,092 records for Ukraine. During tracing it was possible to resolve multiple records for the same individual (5% in Ukraine and 2% in Belarus). Thus the number of individuals was somewhat less than the number of selected records; the dose distribution for these individuals is also shown in Table 1.

Current addresses for potential study subjects were sought through a number of sources, including oblast and raion (administrative districts similar in size to state and county, respectively) internal passport bureaus, military registration and enlistment offices, raion and oblast departments of education, and other information resources, including medical establishments in the localities where these individuals lived in 1986.

The results of the tracing effort are shown in Fig. 2. Individuals were deemed to be ineligible or inaccessible for the study if they had died or moved out of the study area or if they were inaccessible due, for example, to military service or incarceration. It may be possible to recruit those on military service at a later date, e.g. when they are on leave, or when they have completed their service. Potential study subjects who, when contacted, had had a previous diagnosis of thyroid cancer were allowed to participate in the screening process, but they will be excluded from all study analyses. Of the remaining potentially eligible individuals, addresses could not be located or contacts could not be made for 21,171 (57%) in Belarus and 10,307 (34%) in Ukraine. The remaining subjects, 16,213 (43%) in Belarus and 19,612 (66%) in Ukraine, were located and contacted so they could be invited to participate in the study.

#### *Recruitment of Potential Study Subjects*

After the tracing procedures were completed, intensive efforts were made in both countries to recruit the located potential study subjects. Recruitment procedures differed somewhat between the countries due to local considerations of feasibility.

In Belarus, letters were sent to all located potential study subjects explaining the study. A postcard was also included to confirm the subject's identity and place of residence in 1986, with a provisional date and time for the subject to attend for a screening session. The subject was asked to return the postcard by mail to the screening center. The postcard also provided an opportunity for the subject to refuse to participate in the study.

Up to four repeat letters were sent to subjects who did not respond. The current address of those who still did not respond was then rechecked with the Address Bureau to see whether they had recently moved. For those who had moved, the sequence of letter invitations was then repeated.

For subjects invited for screening in the fixed centers in Minsk and Gomel who did not attend for screening at the appointed time, telephone calls and personal visits were made to reschedule appointments and to encourage subjects to participate. For non-attendees resident in more rural areas who were invited to be screened at mobile centers, personal visits were made at the time the mobile team was in the area. This was supplemented by a letter signed by the head of the local medical authority.

In Ukraine, letters of invitation were sent to potential study subjects. These letters were signed by the Minister of Public Health and described the study. A postcard was sent with the letter giving the respondent the choice of being screened by a mobile team or at the fixed center in Kyiv, a choice of dates to attend for screening, and the option to refuse to participate in the study.

Lists of subjects living outside the cities of Kyiv and Chernihiv who did not respond were given to local medical staff who in turn were asked to determine whether these people lived at the address, to contact them and to re-schedule appointments for screening, and to determine reasons for non-response and refusal.

Potential study subjects living in the cities of Kyiv (those who lived in 1986 in Pripjat city and Chornobyl raion) and Chernihiv were contacted by telephone to try to reschedule their appointments. Up to six such calls were made over a period of 2 years. If they had no telephone, people in Chernihiv were contacted in person. In Kyiv the great majority of people possess telephones, so personal contact was not necessary.

Throughout the entire study, advertising of the study using local newspapers and radio broadcasts took place to encourage recruitment.

The results of the recruitment efforts in Belarus and Ukraine are summarized in Fig. 2. Some potential subjects could not be contacted despite intensive efforts, and some of those contacted proved ineligible or refused to participate. The remaining 25,161 (11,918 in Belarus and 13,243 in Ukraine) attended the first screening cycle and thus constitute the cohort.

Table 1 shows the distribution of the cohort by initial dose estimates, and Table 2 shows the distribution of the cohort by gender and age at the time of exposure (i.e. April 26, 1986).

#### *Follow-up of the Cohort*

It is planned to screen the cohort every 2 years (with some groups being screened annually in Belarus), and this process will constitute the basic method of follow-up. Newsletters and greeting cards are being sent to members of the cohort at regular intervals to remind them of their participation in the study. For those who cannot be contacted at the time of the next screening examination, contact information with next of kin and friends collected at the time of first screening will be used as a first means of tracing such individuals. If this fails, the processes used for tracing subjects initially (described above) will be used in an attempt to ensure a minimum loss to follow-up.

Study subjects included in the cohort attended their initial screening examination starting in December 1996 in Belarus and April 1998 in Ukraine (screening cycle 1). All members had been screened at least once by the end of March 2001. Thus the first screening cycle took more than 2 years to complete due to both pilot studies and logistical problems encountered in startup. However, the second cycle ran on schedule in both Belarus and Ukraine and was completed in 2 years (by the end of March 2003).

In Belarus, the majority of subjects are screened every 2 years, but some subjects are screened yearly by order of the Ministry of Health

**TABLE 1**  
**Extended**

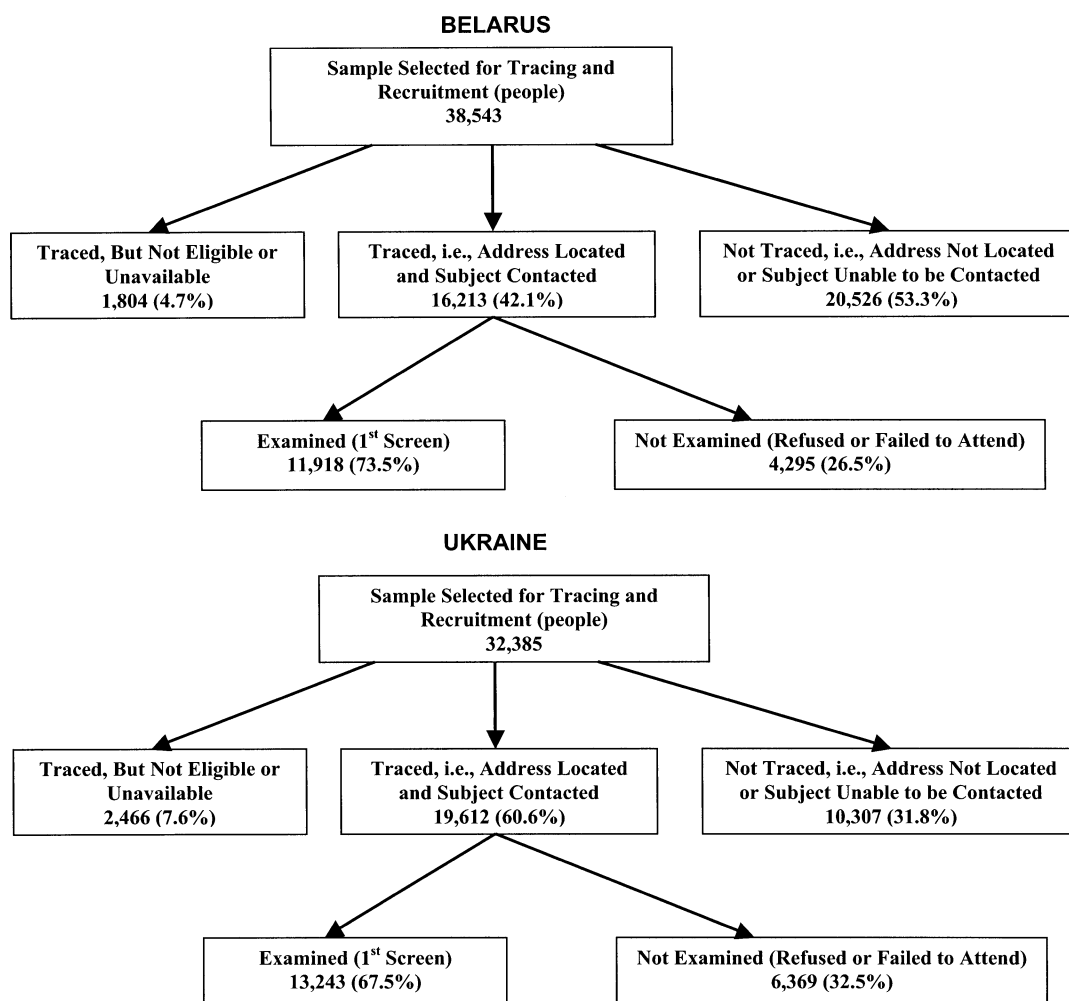
Dose group (Gy)					
Belarus		Total			
$\geq 1.0$	Total	$< 0.3$	$0.3 \leq D < 1.0$	$\geq 1.0$	Total
8,435	39,188	66,264	29,763	18,510	114,537
8,150	38,543	34,954	19,072	16,902	70,928
97%	98%	53%	64%	91%	62%
3,540	11,918	11,140	6,865	7,156	25,161
43%	31%	32%	36%	42%	35%

(those under 18 years of age at the time of screening, those people living in the areas which the Ministry considers highly contaminated, and those evacuated from the 30-km exclusion zone).

Current plans are to screen members of the cohort for a minimum of three screening cycles. When all of the data from the second screening cycle are available for analysis, a decision based on the results of the first two screening examinations, participation rates, feasibility of continued follow-up, availability of funding, and other factors will be made regarding the nature of follow-up of the cohort beyond the third cycle.

#### Overview of the Examination Procedure

The primary objectives of the screening examination are to detect various thyroid disorders in study subjects, in particular thyroid cancer. Screening examinations are conducted at two fixed centers in Belarus (Minsk and Gomel) and a single fixed center in Ukraine (Kyiv) and by mobile teams in both countries that are attached to local polyclinics (out-patient care centers) in the field as their schedules require. All personnel directly involved in the screening examinations are blinded as far as pos-

**FIG. 2.** Summary of tracing and recruitment.

**TABLE 2**  
**Description of Examined Cohorts by Demographic Variables**

	Belarus			Ukraine		
	<i>N</i> ("the cohort")	Percentage ("the cohort")	Percentage (source population)	<i>N</i> ("the cohort")	Percentage ("the cohort")	Percentage (source population)
Total	11,918	100		13,243	100	
Gender						
Female	6,130	51	50	6,275	51	50
Male	5,788	49	50	6,518	49	50
Age on April 26, 1986 (years)						
0-4	3,866	33	24	4,531	34	27
5-9	3,500	29	28	3,936	30	28
10-14	3,109	26	35	3,961	30	26
≥15	1,443	12	12	815	6	18

sible to the subjects' individual thyroid dose estimates. In Belarus, where subjects from highly contaminated regions are screened annually, it is possible that those conducting the screening examinations could be aware that this increased frequency of screening could indicate subjects from higher-dose areas. Any effect of more frequent screening on risk estimates will be examined during the analysis.

At each screening examination, each subject is greeted by a registrar to whom he or she provides informed consent. The registrar then collects information on the current addresses of the subject and close relatives, marital status, education and occupation. The registration process is followed by (1) blood drawing by an annually recertified phlebotomist for laboratory studies, (2) collection of spot urine to determine urinary iodine, (3) thyroid palpation and ultrasound examination by a trained ultrasonographer, (4) medical history and thyroid palpation by an endocrinologist, and (5) dosimetry interview to elicit information on factors relevant to the estimation of individual thyroid dose, e.g. consumption of milk in 1986. For those subjects who were less than 10 years old at the time of the accident, the dosimetry interview is conducted with the mother or a close relative. During the first cycle, different, though similar, questionnaires were used in Belarus and Ukraine. An improved questionnaire, which is identical in the two countries, will be administered to each subject starting in round two. Each subject will complete the new questionnaire once, but the interview load will be spread over cycles two and three for logistical reasons.

At the conclusion of the examination, the subject is given the preliminary results by the endocrinologist.

Study subjects are being referred for fine-needle aspiration biopsy, early recall for re-examination, or recall at the time of the next round of routine screening. They and their medical practitioners are informed of the final result of screening when laboratory tests on blood samples are subsequently completed. Although treatment of thyroid disease is not part of the protocol for the study, all individuals with treatable thyroid disorders are offered standard medical care in the appropriate medical institutions in Belarus or Ukraine. Study subjects are also compensated for their travel expenses for attending screening and for any loss of income incurred by visiting a screening center with a gift package in Belarus and cash in Ukraine.

#### *Ultrasound Examination*

Ultrasound is more sensitive than either palpation or thyroid radionuclide scanning in detecting structural abnormalities in irradiated individuals (21). Physicians with special training and expertise in thyroid ultrasonography carry out an ultrasound examination on each subject. The ultrasonographer performs thyroid palpation and records the findings before carrying out the ultrasound examination. Both lobes of the gland and adjacent neck structures are examined, and normal features and any ab-

normalities are characterized with respect to size, shape, echogenicity, echostructure and other sonographic features. Abnormal findings are recorded either on thermal prints or on digital media. Images are taken at three transaxial locations for each lobe, together with longitudinal images along the longest axis of each lobe, and thyroid gland volume is automatically calculated based on the volume of an ellipsoid ( $0.479 \times \text{length} \times \text{width} \times \text{depth}$ ). The volume of the isthmus is taken into account when its thickness is over 5 mm. Subjects whose age- and gender-specific ultrasound volume is greater than 200% of a standard (unexposed) population are referred for additional medical evaluation.

Quality control of instruments is performed using a multipurpose ultrasound test phantom (ATS Model 550) scanned using the standard probe and ultrasound instrument settings. Systems used in the field are checked prior to use at each location to which they are moved, while fixed systems in other centers are checked less frequently. Quality control of personnel is accomplished by annual recertification of operators by supervisory personnel.

#### *Medical History and Thyroid Palpation*

The endocrinology examination begins with a medical history administered by the endocrinologist; an interval history will be obtained at each subsequent examination. During the first screening cycle, similar questionnaires were used in Belarus and Ukraine, though with a few minor differences. Starting with the second cycle, a common structured and scripted questionnaire is being used in both countries. Information is sought on intake of medications and important food sources of iodine that might influence the development of thyroid disorders, and symptoms suggestive of thyroid dysfunction are elicited. The medical interview is followed by palpation of the thyroid by the endocrinologist. The endocrinologist compares her/his findings with those provided previously by the ultrasonographer. Significant disagreement between the ultrasonographer and endocrinologist is resolved by mutual discussion at the time of screening and, if necessary, by examination by another physician. Examiners are initially certified by direct observation by the chief endocrinologist and then periodically to ensure maintenance of good technique. Procedures are strictly defined, and thyroid enlargement is recorded using the current WHO classification (22).

At the conclusion of the screening examination, the initial findings are reviewed with the patient by the endocrinologist, who is also responsible for making any indicated referrals or arranging for subsequent examinations. A copy of the preliminary or interval evaluation is given to the patient at that time or sent by mail.

#### *Fine-Needle Aspiration Biopsy*

Solitary nodules meeting the criteria in Table 3 are referred for fine-needle aspiration biopsy under ultrasound guidance. Between one and

**TABLE 3**  
**Criteria for Performing Fine-Needle Aspiration Biopsy**

1. Thyroid nodule or focal lesion with largest diameter  $\geq 10$  mm detected by either palpation or ultrasonography
2. Thyroid nodule or focal lesion 5 to 10 mm at least partially solid and with the following indirect signs of malignancy
  - Unclear or irregular borders
  - Extension through thyroid capsule
  - Heterogeneous or hypoechoic ultrasonic density
  - Stippled calcification
  - Increasing size during follow-up
  - Abnormal lymph nodes of uncertain etiology
3. Diffusely abnormal thyroid structure accompanied by unexplained cervical lymphadenopathy. In this case, fine-needle aspiration biopsy of one or more lymph nodes will also be done
4. In the case of indeterminate or non-diagnostic cytology, fine-needle aspiration biopsy will be repeated up to three times within 1 year

three attempts to obtain a satisfactory sample per nodule are made during a single session. In the case of multiple nodules that differ in size, shape or texture, two or three are biopsied, including the most suspicious nodule. If nodules of similar appearance are identified, up to three are biopsied. Enlarged cervical lymph nodes suspicious for metastases are sampled.

Ascertainment bias is minimized by standardized examination and referral procedures, which are done independent of radiation dose. Aspirated material is smeared onto glass slides, air-dried and stained using the Giemsa technique (May-Grunwald-Giemsa or Diff Quik® stain) (23).

Repeat fine-needle aspiration biopsy is performed if the cytology specimen is of inadequate cellularity. If the repeat attempt is still non-diagnostic or inconclusive, the subject is recalled in 3 to 6 months for re-evaluation including a repeat procedure if the nodule persists. Regardless of cytology results, if a thyroid or neck nodule is clinically suspicious for cancer or metastases, the subject is referred directly to surgery.

The cytologist's diagnostic impression of the fine-needle aspiration biopsy smears is designated as either non-diagnostic, non-neoplastic, suspected follicular neoplasm (including Hurthle cell neoplasm), follicular neoplasm, suspicious or positive for papillary carcinoma (with or without prominent follicular features), or suggestive of other malignancy (which is specified). Included in the non-neoplastic category are nodular goiter and thyroiditis, classified as either autoimmune or subacute (granulomatous) thyroiditis. Multiple diagnoses per aspirate and per patient are possible.

Quality assurance includes initial training and certification of physicians performing fine-needle aspiration biopsy, recertification prior to each screening cycle, and direct observation of cytological procedures. Review of the slides by an expert cytopathologist for adequacy and accuracy of diagnosis is conducted at least semiannually.

#### *Further Management of Thyroid Nodules*

If the cytology is diagnostic or suspicious for cancer or neoplasia, the subject is referred either for further evaluation or directly to surgery. The final diagnosis of benign or malignant disease is based upon histopathological examination of surgical specimens and is subject to outside review by a panel of international pathology experts who review all diagnoses for the Chernobyl Tissue Bank (<http://nisctb.swan.ac.uk>).

Because medical and surgical management of thyroid nodules is controlled by the local medical system and not by the project, endocrinologists of the study team ensure that therapy meets accepted clinical criteria and is not influenced by radiation exposure.

#### *Other Thyroid and Parathyroid Diseases*

All cohort members are screened for functional thyroid and parathyroid disorders and for autoimmune thyroiditis. Testing for hypo- and hyperthyroidism is primarily by measurement of serum thyroid-stimulating hormone (TSH) levels, and a free-thyroxine assay is performed when the TSH is abnormal. Clinical evaluation differentiates between subclinical

and overt thyroid disease. Serum antithyroid peroxidase (antiTPO) and antithyroglobulin (antiTG) are the principal tests for thyroid autoantibodies. A diagnosis of autoimmune thyroiditis is reached with varying degrees of certainty by combining antibody titers with TSH concentration and findings on palpation, ultrasound imaging, cytology and histopathology. Thyroglobulin (TG) measurements are performed at every regular screening examination. In addition to being a possible guide to cancer and nodule development, TG has value as an indicator of long-term iodine nutritional status. Disorders of parathyroid function are identified by analysis of serum-ionized calcium. A confirmed abnormal level is followed by assay of parathyroid hormone (PTH) in serum. If the PTH is elevated, further investigation and treatment for hyperparathyroidism are carried out according to local medical practice and may include imaging studies and surgery.

#### *Iodine Nutrition*

Iodine nutritional status is evaluated by measurement of the iodine concentration in random urine specimens collected at the screening examinations. The iodine content of a single, casual urine specimen does not define individual nutritional status, but it was not logistically feasible to carry out an improved sampling procedure (24). Other findings such as diffuse enlargement of the gland on palpation, ultrasound volume, and serum TG levels may be used to indicate prior iodine nutrition.

#### *Laboratory Diagnostic Methods*

Laboratory methods are used to make the diagnosis of thyroid and parathyroid disease, estimate current iodine nutritional status of the cohort, and support medical management. Blood and urine specimens are collected during screening and follow-up encounters at both fixed screening centers and by the mobile teams using similar collection procedures in both countries. To avoid interlaboratory variability in Belarus, specimens from the Gomel screening center and mobile teams are sent to the central laboratory in Minsk for analysis.

Laboratory methods have been standardized and compared across the Ukrainian and Belarussian laboratories. TSH, free T4, TG, anti-TPO antibodies, and anti-TG antibodies are measured with LUMitest® immunochemiluminescence assays from BRAHMS Diagnostica GMBH (Henningendorf, Germany) using a Bertholdt 953 Luminometer (Pforzheim, Germany). Ionized calcium is measured with an ion-specific electrode using a Bayer 634 Electrolyte Analyzer (Leverkusen, Germany) which also measures and adjusts the results for pH; follow-up parathyroid hormone measurements are performed by RIA. Urinary iodine is measured using the method of Dunn *et al.* (25).

The quality of laboratory testing is managed in three ways. First, at the beginning of each analytical run, its acceptability is assessed by running quality control samples provided with the reagents; the acceptability of the quality control results is evaluated with Levey-Jennings charts using laboratory-determined target means and standard deviations (26). Second, the Belarussian and Ukrainian laboratories have enrolled in a

European interlaboratory quality control program to provide external quality control. Third, since the laboratories are using the same methods and quality control materials for all blood tests, a comparison of the control means and standard deviations from each laboratory is used to demonstrate comparability of analytical values. On a periodic basis, the overall means and standard deviations calculated from the individual quality control results from each run are compared between the two laboratories. In the case of urinary iodine, the laboratories use different quality control materials, so instead of the procedure described above, specimens are exchanged between the Belarussian and Ukrainian laboratories and the results compared.

### Dosimetry

The principal aim of the study dosimetry is to provide accurate and precise individual  $^{131}\text{I}$  thyroid doses for all subjects in the examined cohort together with estimates of the uncertainties in individual doses. During direct thyroid measurements for all cohort members taken shortly after the Chernobyl accident,  $\gamma$  radiation emitted by decaying radionuclides was detected by means of scintillators (with or without collimators) or Geiger-Muller counters. The contribution from external irradiation and long-lived internal irradiation was estimated from background measurements. Uncertainty in the estimation of  $^{131}\text{I}$  thyroid activity depends on a variety of factors, including the type of detector, the calibration coefficient of the detector, whether or not a collimator device was used, the method of background measurement, the state of cleanliness of the person examined, stable iodine prophylaxis, and time elapsed between exposure and the measurement. It is expected that use of collimators will result in uncertainties being lower in Ukraine than in Belarus.

Thyroid radiation doses to the subjects have four components: (1) Internal irradiation by  $^{131}\text{I}$ , arising primarily through ingestion of contaminated cow's milk, which is estimated to represent about 90% of the thyroid dose. Because the half-life of  $^{131}\text{I}$  is only 8.05 days, the dose due to this component was delivered within a few weeks of the accident. (2) Internal irradiation from thyroid uptake of short-lived radioiodines (principally  $^{132}\text{I}$  and  $^{133}\text{I}$ ) inhaled during the passage of the radioactive cloud. This component, which is estimated to represent only a small proportion of the thyroid dose for the majority of the cohort members, was delivered during the first week after the accident. (3) External irradiation coming from environmental  $\gamma$ -ray-emitting radionuclides, principally  $^{134}\text{Cs}$  and  $^{137}\text{Cs}$ , which have half-lives of 2 and 30 years, respectively. This component is also estimated to represent a small proportion of the thyroid dose; however, radiation from  $^{137}\text{Cs}$  is still being delivered, at a low rate, and will continue to be delivered over the next few decades. (4) Internal irradiation derived from the intake of  $\gamma$ -ray-emitting radionuclides that do not concentrate in the thyroid. Here again, the most important are the radionuclides  $^{134}\text{Cs}$  and  $^{137}\text{Cs}$ , whose intake results from the consumption of contaminated foodstuffs. This component also is estimated to represent a small proportion of the total thyroid dose and will continue to be delivered at a decreasing rate for several more decades.

Doses from sources 3 and 4 above are, of course, protracted. The doses from these sources will be estimated as far as possible to the end of the study and will be treated as time-dependent in the statistical analysis, in contrast to sources 1 and 2, which will be treated as point exposures in time.

Thyroid dose is reconstructed using the estimated  $^{131}\text{I}$  thyroid activity at the time of measurement in May–June 1986 and a radioecological model to assess the temporal variation of  $^{131}\text{I}$  intake, both before and after direct measurement. The preliminary estimates of  $^{131}\text{I}$  thyroid dose that are presented in Table 1 are based on simplified assumptions: radioactive fallout occurring during a single day, a single pathway of exposure (inhalation for early evacuees and ingestion of fresh cow's milk for most others), and traditional lifestyle and dietary habits. Revised doses are being estimated on the basis of reanalysis of the direct thyroid measurements, a study of radioactive contamination of the environment, development of environmental transfer models (including atmospheric transport and deposition), assessment of individual thyroid volumes at the time

of the accident, information concerning iodine prophylaxis after the accident, and knowledge of individual dietary and lifestyle habits.

The latter two data items are obtained from the dosimetry questionnaires administered to study subjects during the screening examination. During the first screening round, the questionnaires used in Belarus and Ukraine differed somewhat, though both elicited similar information. A new standardized structured and scripted dose questionnaire has now been developed and is being used by both countries during the second and third screening cycles to interview all study subjects. The questionnaire will be administered directly to study subjects who were 10 years old or more in 1986 and to the mothers or to close relatives of subjects who were less than 10 years old. The questionnaire contains questions concerning personal information, place of residence around the time of the accident, consumption of milk/other dairy products, fresh green leafy vegetables, and intake of stable iodine preparations.

The components of the thyroid dose not due to the intake of  $^{131}\text{I}$  will be estimated at a later stage.

Since the estimate of thyroid dose is a function of a number of variables with differing types of distributions, Monte Carlo methods will be used to assess uncertainty in doses.

### Power Estimates

The power of the study to test two hypotheses of primary interest was estimated. The first hypothesis was that of no radiation effect, and the second was that the effect of  $^{131}\text{I}$  was the same as that for external radiation; i.e., the RBE would be 1.0.

To estimate the power, the distribution of dose by gender and age at exposure for the two countries separately was derived from the data on activity measurements. The expected number of cases of thyroid cancer in each dose category (based solely on age and gender distribution in a particular dose group) in the absence of radiation was then estimated by applying the gender- and age-specific thyroid cancer incidence rates from the Belarussian Cancer Registry for the years 1983–1987 (i.e. pre-Chernobyl) to the expected person-years at risk of the two screened cohorts. It was assumed that there will be an average 10% loss to follow-up for each screening round and that, in total, there will be four such rounds.

To model the radiation effect of  $^{131}\text{I}$ , the ERR model proposed by Ron *et al.* (2) from the combined analysis of seven studies of thyroid cancer after exposure to external radiation was used. A range of ERR per gray from 1.0–6.0 was used for different scenarios corresponding to an RBE of 0.17–1.0. The upper value of 6.0 was obtained by applying the model derived from Ron *et al.* (2) to the age-at-exposure distribution of the examined cohort (it should be noted that the age distributions of the examined cohort and the cohort of Ron *et al.* overlap but are not identical). The dose term used for each dose group was the estimated true arithmetic mean derived from the observed preliminary dose distribution by assuming a classical log-normal measurement error model. Thus measurement errors in dosimetry were specified by the log (geometric standard deviation) of the log-normally distributed error term. The value of this parameter was 1.0, the best “guesstimate” of the dosimetrists. This gives an arithmetic average error per individual of about  $\pm 65\%$ .

By using the linear excess relative risk model under the various scenarios, the average number of observed cases in each dose category could then be calculated by multiplying the expected number by the appropriate risk term. A Poisson model was then fitted to these data using the linear excess relative risk model and the true arithmetic mean for each observed dose category (i.e., assuming a correction was applied for measurement error in doses). Score tests were used to test the two main hypotheses of interest against the data that had been generated. The power was then estimated by subtracting the appropriate standardized normal deviate (1.645 for a one-sided test at the  $\alpha = 0.05$  level) from the appropriate score test, and using the inverse normal distribution to obtain the power estimate. The correctness of this approach was confirmed by computer simulations.

It is well established that screening programs in general increase the apparent incidence of disease over the normal background rate, and this

**TABLE 4**  
**Power Estimates (%)<sup>a</sup>**

True excess relative risks per gray <sup>b</sup>	True RBE	Study		
		Belarus	Ukraine	Combined
Power against hypothesis that ERR = 0.0 (i.e. no radiation effect)				
6.0	1	>99	>99	>99
4.0	2/3	>99	>99	>99
2.0	1/3	>99	94	>99
1.0	1/6	>99	65	>99
Power against hypothesis that ERR = 6.0 (i.e. RBE = 1.0)				
2.0	1/3	99	58	>99
1.0	1/6	>99	90	>99

<sup>a</sup> Log geometric standard deviation of the measurement error in dosimetry = 1.0.

<sup>b</sup> Assuming the age-at-exposure distribution of the present cohort.

is certainly true for studies of thyroid cancer induced by external radiation (27). Thus the background incidence rates from the Belarussian Cancer Registry are likely to substantially underestimate the total number of cancers observed in a screening-based study. The power estimates were adjusted to take account of this phenomenon by using the actual number of thyroid cancers observed in the two countries during the first round of screening. It was assumed that these cases represented 2 years of incidence, and the corresponding rates were applied to subsequent screening cycles that will also cover 2 years of incidence.

The above model was then applied to several scenarios representing various true values of the excess relative risk. The results are shown in Table 4, which gives power estimates against both hypotheses.

The combined study has excellent power to detect a radiation effect (first hypothesis) if the RBE is as low as 1/6. To test the hypothesis that the RBE is 1.0, the combined data from the two cohorts under the scenario of an RBE of 1/3 or less again has excellent power.

#### Statistical Analysis

The analysis will focus on fitting dose-response models to the observed data. The basic form of dose-response relationships will be:

$$R_0 \times [1 + (\beta_1 D + \beta_2 D^2) \times e^{(\sum \gamma_i Z_i)}] \quad (\text{multiplicative model}); \quad (1)$$

$$R_0 + [1 + (\beta_1 D + \beta_2 D^2) \times e^{(\sum \gamma_i Z_i)}] \quad (\text{additive model}); \quad (2)$$

where  $R_0$  is the background rate,  $D$  is thyroid dose,  $Z_i$  represent potential modifying factors such as age at exposure, and the  $\beta$ s and  $\gamma$ s and their confidence intervals are estimated from the data. Although linearity seems to hold for external X and  $\gamma$  radiation (2), the possibility of curvilinearity in the data will be investigated through the quadratic dose term. Tests of hypotheses will also be based on this expression.

Expression (1) multiplies the background incidence rate (excess relative risk model), while expression (2) adds to the background incidence rate (excess absolute risk model). The observed data can be fitted to either Poisson regression or proportional hazards models using the EPICURE computer program (28), which will give point and interval estimates and test the significance based on likelihood procedures.

Cancers detected by screening are by definition previously undetected. Therefore, the first round of screening may be regarded as determining the prevalence of previously undetected disease which has occurred over an unknown period. Thus incidence risks cannot be estimated directly from the first-round data. However, the prevalence odds ratio is a very good approximation to the incidence rate ratio provided that the disease in question is rare (ref. 29, p. 165). Thus the first-round data may be fitted to the relative risk model described above and should provide essentially unbiased estimates of the relative risk, but not of the excess absolute risk. In contrast, cases detected during the second and subse-

quent rounds and interval cases can be related to a defined period and thus can be used to estimate both excess relative and excess absolute risks. Thus the overall ERR can be estimated by combining data from all screening cycles including the first, whereas the EAR can be estimated only from data obtained in second and subsequent screenings together with interval cases.

Measurement error in dosimetry will be taken into account by using Monte Carlo simulation.

Separate analyses will be conducted for Belarus and Ukraine. It is expected that the definitive risk analysis will make use of the combined Belarussian and Ukrainian data. In the event, however, that a differential is present in the dose-specific risk estimates of the two arms of the study, the analysis will initially be directed to this differential and its significance.

## DISCUSSION

The establishment of quantitative risk estimates of thyroid cancer after exposure to radioactive iodines, particularly  $^{131}\text{I}$ , is an important issue in both radiation epidemiology and public health. Many individuals are exposed to  $^{131}\text{I}$  for medical diagnostic or therapeutic purposes, and radioactive iodines are potentially an important component of the fallout that would result from any future nuclear power plant accident.

There is epidemiological evidence of the absence of any measurable increase in risk associated with  $^{131}\text{I}$  among adults (30), but the situation in children has yet to be established. Studies of exposure of the thyroid to external X and  $\gamma$  rays (1, 2) have demonstrated that the thyroid is one of the most sensitive organs in its response to such radiation. Thus the sensitivity of the thyroid to exposure to radioactive iodines is potentially of great concern. In the absence of direct empirical evidence, such risks are often estimated by using the results from studies of external  $\gamma$  or X rays together with an assumed RBE. The National Academy of Sciences National Research Council Committee on the Biological Effects of Ionizing Radiation (BEIR V) (31) used this approach, with an assumed RBE of 2/3 based on consideration of the very limited human data and results of animal experiments. However, it would clearly be preferable to derive risk estimates directly from empirical data obtained from epidemiological studies of young people exposed to radioactive iodines.

The Chernobyl accident has had long-term and major effects in health, social and economic terms on the three countries primarily affected, Belarus, the Russian Federation, and Ukraine. However, this disaster has provided what to date is a unique opportunity to directly study the impact of substantial exposure to radioactive iodines on a population of young people. The study described in this paper will take advantage of this unfortunate situation to provide directly measured risk estimates of thyroid cancer from exposure to radioactive iodines. This carefully designed and conducted long-term cohort study of more than 25,000 individuals should result in the most precise risk estimates yet available.

The strengths of the current study include:

1. The large size of the cohort, which, as shown in the section on *Power Estimates*, should lead to adequate tests of the main hypotheses of interest.
2. The high preliminary dose estimates obtained for some study subjects, and the availability of a wide range of doses, including many individuals who received a minimal dose. This again contributes to the power of the study to test the main hypotheses.
3. Individual doses are being estimated, and other potential confounders and effect modifiers are also being assessed at the individual level, thus avoiding the problems of ecological studies.
4. The availability of radioactivity measurements for the thyroid made shortly after the accident for all individuals in the study; this is a major advantage in estimating individual doses with accuracy and precision and thus reduces any potential bias in risk estimates arising from measurement error in doses.
5. The potential confounding effect of screening should be matched out to a great extent since subjects are all being screened to the same extent, irrespective of their dose.
6. The international pathology review should provide independent confirmation of diagnosis to a high degree of accuracy.

As with any study, the present study has limitations which need to be borne in mind and addressed. The principal limitations include:

1. Because of the screening nature of the study, it is possible that some occult thyroid cancers will be detected and possibly included in the analysis. (In this context, "occult" refers to cancers which without being detected by screening would possibly never go on to manifest themselves symptomatically during an individual's lifetime.) The existence and number of such occult cancers is, of course, a matter for speculation, but given the very large increase in incidence after screening (27), it seems likely that such occult cancers do exist. Thus risk estimates from the present study will be for the incidence of such occult cancers combined with those which would progress to become symptomatic and thus would be detected. Truly occult cancers should not be a public health problem but still could, of course, be attributed to a radiation effect. On a relative risk scale, if the same incidence risk applies to occult and non-occult cancers, estimates of the relative risk from a screening study would also be valid for applying directly to non-occult cancers. However, estimates of the excess risk (based on the risk difference) will, of course, be greater if occult cancers are included than if they were not. This caveat needs to be borne in mind when interpreting the results of any screening study.
2. Given the fact that 34% of the originally targeted sample of the source population was actually examined, the possibility of selection bias needs to be considered. The impact of selection bias depends upon which factors are

differentially distributed in the source population and the cohort and the manner in which these factors interact to produce risk of disease. Differences in the dose distribution between the source population and cohort will not bias ERRs or EARs under simple multiplicative or additive models. The other factors known to affect risk of thyroid cancer are age and gender, and, since these will be adjusted in the analysis, they too should not introduce bias because of any differential selection. Although other unsuspected and unmeasured factors could theoretically introduce a degree of selection bias, there are no obvious potential candidates for such factors. A possible exception to this arises because response rate is correlated with dose in Belarus (see Table 1). If this represents a geographic effect (e.g. Gomel compared to Minsk) and iodine deficiency varied by geography, it is possible that such deficiency is related to thyroid disease independently of radiation. This could introduce selection bias with regard to relative risk estimates, though adjustment for iodine deficiency in the analysis of the cohort should address this possibility. It would be possible to assess this potential problem to some extent by comparing incidence of thyroid cancer among the target sample that did not enter the screening study, if such cases were to be completely ascertained. However, this interpretation would be hampered because of lack of knowledge of the screening practices for those individuals who were not examined in the present study.

3. The cohort started being examined at the end of 1996 in Belarus and in 1998 in Ukraine. Thus it will provide no direct knowledge of the risk of thyroid cancer before these dates, i.e. for the first 10–12 years after the accident.
4. There may be inadequate data on prior screening history for study subjects, which has to depend on individual recall. For example, if high-dose subjects received more screening prior to entering the study, this could have removed more cases in the high-dose group than the low-dose group. Similarly, there is a lack of individual data on iodine nutrition since 1986; reliance will have to be made on any available historical data, providing this information by geographical area. Finally, only the current volume of the thyroid will be available on an individual basis. The dose model will have to rely on thyroid volume estimates from other sources and the development of an appropriate model to predict the thyroid volume of study subjects in 1986. Potential sources of data for these three variables are currently being sought.

To date, as a result of the completed first round of screening, approximately 100 histologically confirmed thyroid cancers have been detected in the screened cohort. A few potential cases are still under examination. This number will provide adequate power for testing for a dose-related increase in risk and should provide sufficient numbers to provide a statistically adequate dose-response model. The

accumulation of further cases during the subsequent rounds of screening should both improve the precision of the parameters in the dose–response model and enable a test of the hypothesis that the effect of radioactive iodines differs significantly from the corresponding effect from external X and  $\gamma$  radiation.

In summary, a sufficient number of cases of thyroid cancer have already been accumulated to provide an appropriate dose–response model for radioactive iodines based on far larger numbers of cases and more accurate and precise dose estimates than have generally been available to prior analytical epidemiological studies. Continued screening and follow-up of this cohort should yield more precise estimates of the parameters of such a model. Similar considerations apply to the study of benign nodules, hypothyroidism, autoimmune thyroiditis, and hyperparathyroidism. Further, this study will provide information on differences and similarities between the effects on thyroid diseases of external radiation exposure and radioactive iodines and contribute useful information to both the relevant radiation epidemiology and public health issues.

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